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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 08/078,768
Filing Date: June 16, 1993
Appellant(s): TULLIS, RICHARD H.

Felicity E. Groth
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed October 18, 2004.

(1) *Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

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(2) *Related Appeals and Interferences*

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) *Status of Claims*

The statement of the status of the claims contained in the brief is correct.

(4) *Status of Amendments After Final*

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) *Summary of Invention*

The summary of invention contained in the brief is correct.

(6) *Issues*

The appellant's statement of the issues in the brief is correct.

(7) *Grouping of Claims*

The rejection of claims s 64-76 and 78-83 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) *Claims Appealed*

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art, Post-Filing Date Art of Record, and Patented File Records

- (a) Tullis, U.S. Patent No. 5,023,243
- (b) Tullis, U.S. Patent No. 5,919,619
- (c) Tullis WO 83/01451 (April 28, 1983)
- (d) Stenesh, 1989, Dictionary of Biochemistry and Molecular Biology, Second Edition, John Wiley & Sons, New York, page 226
- (e) Mercola et al, Cancer Gene Therapy 2 (1), 47 (1995)
- (f) Miller et al, Biochemistry 16: 1988 (1997)
- (g) Gura, Science 270: 575 (1995)
- (h) Hijiya et al, Proc. Natl. Acad. Sci. USA 91: 4499 (1994)
- (i) Rojanasakul, Adv. Drug Delivery Res. 18: 115 (1996)
- (j) Tullis et al, Biotechnology International (1992)
- (k) Crooke, Bio/Technology 10: 885 (1992)
- (l) Branch, TIBS 23: 45 (1998)
- (m) Summerton, J. theor. Biol. 78: 77 (1979)
- (n) Crooke et al, Annu. Rev. Pharmacol. Toxicol. 36: 107 (1996)
- (o) U.S. Patent No. 5,023,243, patented file paper no. 9, filed February 9, 1984.
- (p) U.S. Patent No. 5,023,243, patented file paper no. 12, interview summary record, November 15, 1984.
- (q) U.S. Patent No. 5,023,243, patented file paper no. 14, filed December 7, 1984.
- (r) U.S. Patent No. 5,023,243, patented file paper no. 17, interview summary record, October 18, 1985.
- (s) U.S. Patent No. 5,023,243, patented file paper no. 21, filed April 4, 1986.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims.

Claim 71 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,023,243. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of U.S. Patent No. 5,023,243 is a specific embodiment of the generic method of claim 71 in the instant application. Appellant's argument (Brief filed October 18, 2004, pages 18-19) is not convincing because claim 1 of U.S. Patent No. 5,023,243 is not so broad as appellant asserts. Claim 1 of '243 states that the oligodeoxyribonucleotide that is used in the process of selective inhibition of protein synthesis has "a nucleotide sequence substantially complementary to at least a portion of the base sequence of messenger ribonucleic acid coding for said targeted protein". Thus, claim 1 of '243 requires an antisense agent that is complementary to at least part of the coding region of the mRNA to be downregulated. Appellant's assertion that claim 1 is broader than that in that any part of the mRNA may be targeted by the antisense oligodeoxyribonucleotide is not convincing or correct. It is noted that this is the first time in this record that appellant has made such an argument in connection with construing claim 1 of '243 so broadly. It is further noted that the file wrapper history in U.S. Patent No. 5,023,243 does not resemble appellant's current construction of the claims in U.S. Patent No. 5,023,243. For example, see the interview summaries for November 15, 1984 and October 18, 1985, wherein it is indicated that the claims are drawn to the use of oligonucleotide antisense agents complementary to the polypeptide coding region of mRNAs. In addition, in paper no. 14 (filed 12/7/1984) at page 12, lines 26-32, applicant stated,

"Even more importantly, perhaps, Applicant hybridizes his oligonucleotides to the coding region of an m-RNA in order to inhibit protein synthesis, which was not known in the prior art. In the amendment filed previously by Applicant, the claims were amended so that all claims involve targeting the oligonucleotide against the coding region of an m-RNA."

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On pages 13-15 of paper no. 14, applicant goes on to point out this difference between the claimed invention and the prior art that had been applied to the claims (the prior art downregulated protein synthesis by hybridizing oligonucleotides to non-coding regions of mRNA). Later in prosecution, applicant affirmed the claims to be limited to the use of oligonucleotides targeted against the polypeptide coding region only of mRNAs (paper no. 21 (filed April 4, 1986), lines 4-7).

“Moreover, the claims have been limited to oligodeoxyribonucleotides binding to mRNA sequences in the coding region so as to permit inhibition of synthesis of specific targeted proteins.”

In view of appellant's own admissions in connection with the narrow construction of all the claims in U.S. Patent No. 5,023,243 in connection with the targeting of the oligonucleotides to polypeptide coding regions of mRNAs, appellant's arguments in the Brief filed October 18, 2004 are not convincing.

Claims 64-76 and 78-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited to the preparation of stabilized forms of oligodeoxyribonucleotides that are phosphotriesters, does not reasonably provide enablement for all stabilized forms of oligodeoxyribonucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Appellant asserts (Brief filed October 18, 2004, page 7, last full paragraph) that the instant application contemplates, enables, and claims the use of *in vivo* antisense using double stranded oligomers. This assertion is not convincing because the instant application does not disclose the use of double stranded antisense agents. The application throughout refers to the “hybridization” of the antisense agent to its target (*e.g.*, see instant application at: page 3, lines 11-21; page 4, lines 19-23; page 4, line 24 through page 6, line 2; page 8, line 24 through page 9, line 4; page 9, lines 5-14; page 10,

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lines 16-23; and Examples 1 and 2 (*i.e.* pages 12-19). The term "hybridization" refers to the formation of a double stranded nucleic acid by annealing of two single stranded molecules (see Stenesh, page 226, definition number 1 for "hybridization"). For a double stranded antisense agent to work, a triplex would need to be formed. The instant application does not disclose the formation of triplexes. Appellant's reliance upon Mercola et al (Cancer Gene Therapy 2(1), 47-59 (1995)) to complete the application is not convincing because appellant has not established that what is disclosed in Mercola et al is what is taught in the instant application. In addition, Mercola et al was published more than thirteen years after the effective filing date of the instant application. There is simply no disclosure, explicit or implicit, in the instant application that the claimed invention can be carried out using double stranded oligodeoxyribonucleotides as antisense agents. Appellant does not discuss what sort of guidance the application provides for those of skill in the art if the mechanism of action for the oligodeoxyribonucleotides mentioned in the claims is not disclosed.

The Declaration (executed June 14, 2002) by Dr. Crooke is not persuasive for the following reasons.

- (a) Section 3, last paragraph is not persuasive because it relates an opinion only. No actual search query or search results are disclosed, nor there established what would be a reasonable or likely search query by one of skill in the art as of the effective filing date (October 23, 1981). The Brief filed October 18, 2004, while alluding to part 3 of the Crooke declaration (Brief filed October 18, 2004, paragraph bridging pages 9-10) does not indicate any particular query or search results that might be expected from such an imaginary search.
- (b) In section 5a the issue is misrepresented. The record contains no comment from the examiner as to the "inventive principle" regarding selection of the form of stabilized oligonucleotide to be used. The "point of novelty" is irrelevant in relation to a rejection under 35 U.S.C. § 112, first paragraph. The targeting of the coding region is not at issue in this application.

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- (c) Regarding section 5b, declarant's comments in connection with what one of skill in the art would have been led to based on the mere reference to Miller et al in the application (Biochemistry 16: 1988 (1977)) and what Miller et al (1977) in turn refers to, can be speculation at best and is for that reason most unpersuasive. It is noted that declarant points to no statement in the application as filed that would lead one of skill in the art to use any of the referenced material in Miller et al (1977). Indeed, Miller et al (1977) is not even incorporated by reference in the instant application. Reading the context in which Miller et al (1977) is used (see the instant application at page 17, lines 21-25), it is not understood why one of skill in the art would look to Miller et al (1977) (let alone a reference (Eckstein et al, Angew. Chem., Int. Ed. Engl. 6: 949 (1967)) referred to by a work referenced (Miller et al, Biochemistry 13: 4888 (1974)) by Miller et al (1977) for some form of modified oligonucleotides other than the phosphotriesters that Miller et al (1977) discloses and that the application points to Miller et al (1977) for. Declarant's statements regarding a "routine search" of the literature is not persuasive because it is the application that is to be enabling, not further searching and extrapolation by those of skill in the art. Furthermore, it has not been established in this record that all of the stabilized forms of oligonucleotides that are disclosed in the prior art actually work *in vivo*. It is noted that appellant has not discussed this assessment of the Crooke declaration in the Brief filed October 18, 2004.
- (d) In section 5b at page 6 declarant states "application provides adequate guidance as to which stabilized oligonucleotides to use in the invention". This assertion is most unpersuasive in the absence of an indication as to where the instant application provides such a teaching. The only disclosure regarding this is the reference to Miller et al (Biochemistry 16: 1988 (1977)) at page 17 21-24 and

this reference is to the production of phosphotriesters. A patent to a method of oligonucleotide directed inhibition of expression using phosphotriesters has already been issued to appellant (Tullis U.S. Patent No. 5,023,243). Additionally, implied in this statement (section 5b, page 6) is that not all stabilized oligonucleotides ought to be used in the invention. If that is the case, then the application as filed is deficient in not providing guidance to those of skill in the art as to which stabilized form or forms to use. That others had synthesized some forms of oligonucleotides (see the references cited in section 5b) does not convince that the application teaches or points one of skill in the art to the potential use of those forms of modified oligonucleotides in the claimed methods. It is noted that appellant has not discussed this assessment of the Crooke declaration in the Brief filed October 18, 2004.

- (e) In section 6a declarant states, "the stabilized oligonucleotide is simply administered" yet there is no teaching of how to administer any of the oligonucleotides. It is noted that appellant has not discussed this assessment of the Crooke declaration in the Brief filed October 18, 2004.
- (f) Section 6b deals with uptake of oligonucleotides in culture, but that is not an issue here. Appellant already has a patent that claims that subject matter (Tullis U.S. Patent No. 5,919,619).
- (g) In section 6b, page 7, declarant's *ad hominem* remarks in connection with Gura (Science 270: 575 (1995)) are given no weight. Declarant has demonstrated no competence in regard to whom Gura did or did not interview for the Science article. Declarant has not gainsaid the substance of the Gura article.
- (h) Declarant's arguments in section 6b, pages 7-8 are most unconvincing. Of the four articles mentioned in that section, only two are of record (Mercola et al and Putnam et al). The arguments related to Mercola et al are not convincing

because all of the references cited by Mercola et al were published long after the effective filing date of the instant application. For example, declarant makes much of the references cited by Mercola et al at pages 54-55, yet none of those references was published prior to 1992 (all were published in 1992, 1993, or 1994). Similarly the references cited by Putnam on pages 154 and 156 (pointed to by declarant) were published in 1993 and 1994. Declarant and appellant have not established for this record whether any of the methods used in either of the references in the record or those referred to by those references (this method of second-hand citation of references to provide evidence is of little value in establishing fact) are comparable to anything taught or disclosed in the instant application. Accordingly, these arguments are not convincing. Declarant also discusses Hijiya et al (Proc. Natl. Acad. Sci. USA 91: 4499 (1994)). Declarant discusses Hijiya et al to teach the inhibition of the MYB gene *in vivo* in mice by the use of oligonucleotides. This is in fact disclosed in the reference, however, the reference does not include certain details such as the length of the oligonucleotides used, the number of different oligonucleotides that may have been used, and whether the oligonucleotides used were complementary to the coding region of the MYB gene. Additionally, Hijiya et al concludes (page 4503, last paragraph of the text):

Knowledge concerning DNA uptake mechanisms, intracellular ODN [oligodeoxyribonucleotide] trafficking, mRNA disruption mechanisms, and, of equal importance, how apparent resistance develops will all contribute significantly to the effective pharmaceutical use of these compounds. Accordingly, while this area remains in its scientific infancy, the *in vivo* studies and those of our colleagues . . . convince us that modulation of gene expression with antisense DNA is a therapeutic strategy worth pursuing.

If the science of antisense inhibition of expression *in vivo* was in its infancy in 1994, one is left to wonder what the state of the art was in 1981. Hijiya et al

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also echoes the issues that have been long standing in this application, *viz.* uptake, intracellular trafficking [degradation], and interactions with target mRNA [specificity of hybridization] (see page 4500, right hand column and page 4503, last paragraph of text). Hijiya et al, Gura and Rojanasakul (Adv. Drug Delivery Rev. 18: 115 (1996) are not alone since Mercola et al (Cancer Gene Therapy 2 (1), 47-59 (1995)) at page 54 in a discussion of oligonucleotide delivery *in vivo* says:

Are oligodeoxynucleotides a feasible means of delivering an antisense-based compound and is there concordance between the results for antisense oligodeoxynucleotides and plasmid-derived antisense RNA? Human and animal trials of oligodeoxynucleotides are in their infancy and comparisons among approaches are sparse, however, several signposts are available.

Again, the science is in its infancy, but now in 1995.

- (i) Section 6c is not persuasive because declarant does not establish all modified oligonucleotides to be stable *in vivo*. That some are stable is not at issue. The question is what the application as filed teaches one of skill in the art in connection with which stable forms of oligonucleotides are available and which will operate as claimed. It is noted that declarant mentioned, but did not discuss how Rojanasakul was used in the rejection.
- (j) In section 6c declarant claims that the examiner "relies on Gura to support his contention that stabilized oligonucleotides do not hybridize". This is simply incorrect. The issue is what the application teaches what effect the stabilization of oligonucleotides has on the specificity of hybridization (a difficulty with the method that is brought out by both Gura and Rojanasakul and now Hijiya et al). It is the examiner's position that the application does not provide adequate guidance for one of skill in the art to practice the claimed invention in its full

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scope without resorting to undue experimentation for reasons that have been discussed at length in this record.

- (k) It is noted that declarant did not address the issue of the breadth of claims 62-70 and 72 in that these claims embrace a method that does not require the use of stabilized oligonucleotides at all.

Appellant mentions the factors outlined by the U.S. Court of Appeals for the Federal Circuit (*In re Wands* (8 USPQ2d 1400, Fed. Cir. 1988)). They are listed here in the order that appellant stated them (Brief filed October 18, 2004, page 6).

Wands Factor 8 (the breadth of the claims): The first factor involves the breadth of the claims. It is noted here that all of the claims are drawn to a method of inhibiting the production (*i.e.* downregulating) of a protein without inhibiting the expression of other proteins *in vivo*. For the record, here *in vivo* means in a living organism and not inside living cells in culture. In some of the scientific literature, the term *in vivo* may be used to describe a process in living cells in culture conditions. That is not the case here. The term *in vitro* may be used to describe processes in living cells in culture or processes in a cell-free environment. The meanings of these terms are usually clear when taken in context within a given document. The instant application uses the term *in vivo* to describe both the use of the method in an organism and in cells in culture (*e.g.*, see Example 1 beginning on page 12 of the instant application). For purposes of this Examiner's Answer, the terms are used like this: "*in vivo*" means in an organism, "*in vitro*" means in a cell-free system, "in cell in culture" means in cells grown outside of a complete organism on some sort of artificial medium. The requirement for the claims to selectively inhibit the expression of a single protein *in vivo* without inhibiting the expression of other proteins needs to be kept in mind when considering any of appellant's arguments. The Brief filed October 18, 2004 does not contain a discussion of this matter.

Wands Factor 4 (the nature of the invention): This is an invention that is carried out inside a living organism, a self-evidently complex system. The Brief filed October 18, 2004 does not contain a discussion of this matter.

Wands Factor 5 (the state of the prior art): Appellant argues (Brief filed October 18, 2004, pages 8-10) in connection with this factor at length and asserts that the state of the prior art provides for the availability of stabilized oligonucleotides. This is not in question. What is in question is whether the use of any stabilized oligodeoxyribonucleotides, other than phosphotriesters (for which appellant has already obtained a U.S. Patent and which are used in the two working examples of the instant application), is enabled by the instant application. Appellant asserts that no undue experimentation would have been necessary for one of skill in the art to practice the full breadth of the claimed invention. Appellant acknowledges (Brief filed October 18, 2004, paragraph bridging pages 9-10 and first full paragraph on page 10) that the instant application does not exemplify the use of stabilized oligodeoxyribonucleotides other than phosphotriesters.

Wands Factor 6 (the level of one of ordinary (sic) skill, the court listed this as "the relative skill of those in the art"): The relative skill of those in this art is certainly high; one of skill in the art probably possessing a Ph.D. degree in molecular biology, biochemistry, or chemistry and having some years of post-doctoral research experience. Appellant argues that one of skill in the art would have been aware of several forms of stabilized oligonucleotides by searching the literature and by referring to references referred to by a reference referred to in the application.

Wands Factor 7 (the level of predictability in the art, the court listed this as "the predictability or unpredictability of the art"): Appellant argues (Brief filed October 18, 2004, pages 10-17) that the art is predictable and alludes to publications filed after the effective filing date of the instant application (*i.e.*

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October 23, 1981) and declarations already in this record (by Drs., Schwartz, Ruth, and Crooke) to support the notion of predictability in the art of specific *in vivo* antisense inhibition of protein synthesis.

Wands Factor 2 (the amount of direction provided by the inventor, the court listed this as "the amount of direction or guidance presented"): Appellant argues that the application refers to enough for one of skill in the art to be able to practice the claimed invention without performing undue experimentation but does not point to text or other information in the application itself that may guide or direct one of skill in the art in the practice of the claimed invention.

Wands Factor 3 (the existence of working examples, the court listed this as "the presence or absence of working examples"): Appellant points to working examples that include the use of phosphotriester oligonucleotides as antisense agents in cells in culture (*i.e. in vitro*). Appellant has two U.S. Patents (5,023,243 and 5,919,619) that already claim these aspects of the invention.

Wands Factor 1 (the quantity of experimentation needed to make or use the invention): Appellant argues at length (Brief filed October 18, 2004, pages 7-17) that no undue experimentation is necessary for one of skill in the art to practice the claimed invention. The arguments are accompanied by declarations and post-effective-filing-date publications.

Appellant asserts that one of skill in the art would be able to practice the claimed invention using the application as a guide. This assertion most unconvincing as explained below.

Appellant asserts that the application provides adequate guidance for one of skill in the art to use any form of stabilized (against degradation by nucleases) oligonucleotide in the claimed invention. Appellant asserts (*e.g.*, Brief filed October 18, 2004, page 7) that the application even supports the use of unmodified oligonucleotides (*i.e.* the phosphodiester form) *in vivo*. Appellant had previously argued (paper no. 33, filed April 17, 1995, section C, pages 12-14) that the examiner misinterpreted a statement made by the inventor during the prosecution history of a prior application. Appellant's argument is

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unconvincing in the face of the simple, direct, and unambiguous language used by the inventor.

Appellant's arguments are further unconvincing in view of published statements under the name of the inventor and others. For example, in the publication by Tullis et al (Biotechnology International, 1992, reference A15, already of record (see 11 page reference filed December 15, 2003 in this record)) states on page 79 that one of the key events in the development of antisense technology was the development of more efficient systems for the synthesis of normal and phosphorous modified oligodeoxyribonucleotides and then goes on to cite a number of references, all of which were published subsequent to the effective filing date of the instant application. (The Beaucage et al reference is listed as being published in 1980 at page 79, but is listed as published in 1984 in the bibliography. The 1984 date is almost certainly correct because the Beaucage et al reference is a European Patent application that was filed in 1982.) Additionally, at page 80 (top part of the right hand column), Tullis et al mentions problems with uptake and stability of unmodified oligonucleotides and gives no clue to the reader to do any of the things that appellant now asserts would have been obvious to anyone of skill in the art in 1981. Thus, the evidence in the record shows that appellant himself did not know that unmodified oligonucleotides could be used as antisense agents even as late as 1992. The Brief filed October 18, 2004 does not mention the statements of Tullis et al. Appellant's argument citing Example 1 as basis for the use of the claimed method utilizing unmodified oligonucleotides (paper no. 73, filed June 21, 2002, page 11) is not convincing because Example 1 is limited to the use of the method in cells in culture. Thus, the remarks of Tullis stating that, "Zamecnik and Stephenson used an unprotected oligonucleotide, which would break down *in vivo* before having the desired effect" (see the file wrapper for U.S. Patent No. 5,023,243, paper no. 9, filed February 9, 1984, page 3) are still relevant (the method of Zamecnik et al uses unmodified oligonucleotides as antisense agents in cells in culture). There is no evidence in the record to show that appellant conceived of or disclosed the use of unmodified oligonucleotides as antisense agents as of the effective filing date of the instant application.

Appellant further argues that the application need not teach what is known in the art (Brief filed October 18, 2004, pages 7-10). This is correct; however, the application not only does not teach what

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was not known in the art, but a number of post-effective-filing-date references in this record show that much was not known about this art and that much experimentation was needed to make the claimed method work even more than a decade after the effective filing date of the application. Appellant asserts that phosphotriester oligonucleotides are simply a representative example of the stabilized oligonucleotides (Brief filed October 18, 2004, pages 7-8). This assertion is not persuasive because the phosphotriester oligonucleotides are the only disclosed example of stabilized oligonucleotides in the application. There is no disclosure of any other particular form of stabilized oligonucleotide, nor is there a hint of how the stabilized form may affect the specificity of hybridization *in vivo*, a crucial aspect for the proper operation of the claimed invention. This is relevant to the issue of enablement here because the purported mechanism of action (*i.e.*, nucleic acid molecular hybridization of the target mRNA to a single stranded oligodeoxyribonucleotide antisense agent) provides crucial "guidance" to those of skill in the art in the practice of the claimed invention. At least in the case of the use of double-stranded oligodeoxyribonucleotides, appellant himself (Brief filed October 18, 2004, page 7, last three lines) warns us that he has not disclosed the mechanism of action. Just how such a lack of disclosure provides guidance to one of skill in the art wishing to downregulate a specific mRNA without decreasing translation from other mRNAs (a requirement for all of the claims) remains a puzzle.

In a review by Crooke (Bio/Technology 10: 885 (August 1992)), it is stated (page 885) that,

Methylphosphonates appear to have lower therapeutic indexes. Too few data are available to draw conclusions about other classes of oligonucleotides. . . . Very few data support putative mechanisms of action, and generalizations concerning desired mechanisms of action are not possible. Nevertheless, a variety of mechanisms of action may be employed by oligonucleotides to result in significant biological activities.

Thus, even nearly eleven years after the effective filing date of the instant application, it was not possible for those of skill in this art to make generalizations concerning the mechanisms of action of oligonucleotides. That being so, how can the instant application correctly be said to fairly teach those of skill in the art how to practice the full breadth of the claims? It is noted here that the instant disclosure

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had been published as WO 83/01451 on April 28, 1983 and so the method of appellant was available to those of skill in the art at least as early as that date. Appellant further argues (Brief filed October 18, 2004, page 9, first full paragraph) that references of record support the notion that other forms of stabilized oligodeoxyribonucleotides suitable for use in the invention were known in the art as of the effective filing date of the application. This is an overstatement because the application itself refers to one reference that discloses the use of phosphotriesters (Miller et al, Biochemistry 16: 1988 (1977)) which in turn refers to a second reference dealing with phosphotriesters (Miller et al, Biochemistry 13: 4888 (1974), which in turn refers to Eckstein et al (Angew. Chem., Int. Ed. Engl. 6: 949 (1967)). This chain of referencing is discussed in the Crooke declaration (item 6) without giving any reason why or how one of skill in the art would be lead to Eckstein et al and why one of skill in the art would combine Eckstein et al with the instant application (if Eckstein et al were so closely connected to the instant invention, it is not clear why Eckstein et al was not directly cited in the application itself). Both Miller et al references refer to a number of other works, so it is unclear why this one would appear so important to one of skill in the art. Neither the Crooke declaration, nor appellant's arguments in the Brief point to any context in Miller et al (1977) that would lead one of skill in the art to Miller et al (1974) or any context in Miller et al (1974) that would lead one of skill in the art to Eckstein et al. Appellant goes on (Brief filed October 18, 2004, paragraph bridging pages 9-10) to assert that one of skill in the art would run literature searches to find more forms of stabilized oligonucleotides that might be suitable for use in the claimed method. This argument is not convincing because the record does not contain an example of a plausible search or the results of such a search. This is an observation and not an invitation to submit such a search or search results subsequent to an Examiner's Answer. Additionally, it is the application that is to teach one of skill in the art how to make and use the invention. In view of the difficulty that others have encountered in getting methods embraced by the claims to work (the earliest published account being in 1992), it is evident that those of skill in the art did in fact need to perform undue experimentation (it was and is an active field of research with many highly skilled artisans and a great

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amount of resources) to get the claimed invention to work. The application is, at best, an invitation to experiment.

Appellant argues that the instant application enables the use of oligonucleotides *in vivo* (Brief filed October 18, 2004, pages 10-17) and dismisses the various pitfalls and demonstrated (as published) difficulties in achieving antisense inhibition of expression of a specific polypeptide *in vivo* as being able to be solved by routine experimentation. These arguments are most unconvincing. First, the USPTO has made no requirement in this record for every embodiment of the invention be disclosed or taught (Brief filed October 18, 2004, page 10). There is in fact no method of *in vivo* antisense use taught in the application. Rather, what is described is a goal, not a method *per se*. It is understood that some experimentation may be necessary to practice a claimed invention and such routine experimentation shall not impede patentability. What the instant claims require of those of skill in the art is undue experimentation. Appellant again points to the phosphotriester example in the instant application (Brief filed October 18, 2004, page 10, first full paragraph). It is reiterated that appellant already has a patent that covers the use of phosphotriester oligonucleotides as antisense agents. Appellant then asserts that only routine experimentation is required to determine which oligonucleotides work in the invention in view of the examples provided in the application. This assertion is not convincing in view of the discussion in the previous Office actions (mailed December 17, 2001 and September 10, 2002) and hereinabove and in view of what is disclosed in Branch (TIBS 23: 45 (February 1998)). Branch confirms and echoes some of the difficulties with the method as outlined in Rojanasakul and Gura as discussed in the Office action mailed December 17, 2001. The following quotes are from Branch.

they [antisense molecules] are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven. Furthermore, a wide variety of unexpected non-antisense effects have come to light. (Abstract)

when an antisense molecule causes a biological effect, it can be extremely difficult to determine whether the change occurred because the reagent interacted specifically with its target RNA, or because some non-antisense reaction -- involving other nucleic acids or proteins -- was set in motion. (page 46, right hand column)

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quantitative data about the magnitude of antisense-induced side reactions are limited, (page 47, left hand column)

An antisense molecule is typically taken to be 'specific' if two criteria are met: (1) there is no gross loss of cell viability, and (2) the levels of the target RNA and its associated protein fall much more than those of the control RNAs. However, this type of experimental design is too limited in scope to provide information about global changes in the RNA and protein populations. (page 47, left hand column)

So far, the concept that an antisense molecule can selectively knock out a single gene appears to have been untested. In the future, several techniques, in addition to two-dimensional gel electrophoresis, might be employed to investigate antisense specificity. (page 47, center column)

The ratio of intended to unintended hits will depend on a complex and unpredictable combination of factors that determine whether the antisense molecule and the potential targets co-localize and whether the complementary sites in the RNAs are buried under proteins or are involved in intramolecular bonds that make them inaccessible. (page 48, center column)

Because it is very difficult to predict what portions of an mRNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells. (page 49, left hand column)

Since accessibility cannot be predicted, rational design of antisense molecules is not possible. (page 49, center column)

The relationship between accessibility to ODN [oligodeoxynucleotide] binding *in vitro* and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored, and will continue to be an active area of research in the future. It is not yet clear whether *in vitro* screening techniques of the sort used by Milner and co-workers [Milner et al, Nat. Biotechnol. 15: 537 (1997)] will identify ODNs that are effective *in vivo*. (page 49, right hand column)

These passages speak for themselves and counter appellant's assertions that "One having ordinary (sic) skill in the art need only have substituted for the phosphotriester oligonucleotides of Appellant's examples other known forms of stabilized oligonucleotides to determine their efficacy in the invention. This would not have required undue experimentation on the part of an artisan of ordinary (sic) skill." (Brief filed October 18, 2004, page 10). In addition, appellant's assertion that, "nothing beyond routine experimentation was required to administer the antisense oligonucleotides under *in vivo* conditions and detect a downregulation in the expression of a specific protein" (Schwartz and Ruth declarations quoted

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in paper no. 73, filed June 21, 2002, page 20) disagrees with the Branch publication. Likewise, the Crooke declaration (item 6a) is at odds with the Branch article in stating

Nothing more than routine experimentation was necessary to use the stabilized oligonucleotides known in the art in October 1981 in the invention. The methods for using different stabilized oligonucleotides according to the invention are essentially identical to the methods for using phosphotriester oligonucleotides set forth in the application. The stabilized oligonucleotide is simply administered, and the expression of the target protein is monitored. This experimentation was routine for one of ordinary skill in the art in 1981.

The Branch quotations above indicate that such monitoring cannot be used as an indicator of downregulation of expression of a single protein *in vivo*.

Appellant asserts that, "A demonstration of F.D.A. acceptable clinical safety is not required by the first paragraph of 35 U.S.C. § 112. Enablement does not require that the claimed invention satisfy the higher safety standards applied to drugs to be used in clinical trials." (Brief filed October 18, 2004, paragraph bridging pages 11-12). The examiner has made no such requirement, implies no such requirement, does not implicitly assert that any such requirement exists for patentability, and shall not make any such requirement. Therefore, appellant's remarks (Brief filed October 18, 2004, pages 11-12) in response to the perceived requirement are given no weight at all.

Appellant argues that the specification provides adequate guidance regarding cellular uptake of oligonucleotides *in vivo* (paper no. 73, filed June 21, 2002, pages 21—25). Appellant cites Summerton (J. theor. Biol. 78: 77 (1979)) to disclose the uptake of both RNA and DNA by animal cells, yet at page 84 Summerton reports,

Double-stranded DNA is also taken up readily with newly-taken-up homologous DNA remaining undegraded substantially longer than heterologous DNA. Single-stranded DNA is generally reported not to be taken up or to be taken up much slower than double-stranded DNA.

Since single-stranded oligonucleotides are required for the instant claims (double-stranded oligonucleotides will not work because they are not free to hybridize to the target mRNA) the problem of uptake remains. Appellant also cites Zamecnik et al (1979) to support the notion of cellular uptake of

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oligonucleotides being well known. However, Zamecnik et al (1979) deals with cells *in vitro* (*i.e.* in cell culture conditions) and not *in vivo* (*i.e.* in an organism). A U.S. Patent to methods of antisense inhibition of protein expression in cells in culture has been issued to appellant. Appellant has provided no data to show the equivalence of uptake of oligonucleotides in cells in culture to be the same as or similar to the uptake of oligonucleotides *in vivo*. Appellant complains that the examiner has not given reasons for a conclusion of a lack of correlation for an *in vitro* (cell culture) or *in vivo* animal model (paper no. 73, filed June 21, 2002 page 22). This is incorrect. Rojanasakul has long been cited by the examiner in this record as supporting the idea that *in vivo* antisense methods are plagued by such problems as: uptake, degradation, and specificity. That results in cell culture conditions cannot be translated to *in vivo* systems is seen in Rojanasakul at, for example page 118.

3. Can antisense work in living systems?

There are numerous studies demonstrating the effectiveness of antisense ONs [oligonucleotides] in various cell culture systems. However, several key questions remain, the most obvious one being "Can the antisense approach work *in vivo*?" This question has often been posed in different forms depending on the background of the person asking the question. From a drug delivery standpoint, the key question is often addressed like "How can antisense ONs be targeted to diseased cells, sparing normal cells?" or "How can antisense ONs be effectively delivered into the intracellular target sites where they can then exert their action?". The first question may be readily answered with the following postulate. If the antisense ONs exhibit no cellular toxicity or non-specific antisense activity, then targeting at the cellular level would not be necessary; that is, all cells could be exposed to antisense ONs. In principle, the exquisite specificity of antisense ONs implies that these compounds are less likely to cause toxic side effects in comparison to conventional drugs. However, several recent studies appear to suggest that cellular toxicity and non-specific activity of antisense ONs can occur (albeit in cell culture systems). . . . To demonstrate antisense activity, ONs that are not complementary to the target RNA are usually used as controls. An antisense activity is implicated if the antisense ON inhibits better than the controls. However, frequently the control ONs inhibit as well or better than the antisense ON Non-specific toxicity of antisense ONs has also been suggested as a result of their degradative products in different cell types, particularly the hematopoietic cells. . . .

The second question "How can antisense ONs be effectively delivered into cells?" is equally difficult to answer. Most antisense ONs are poorly taken up by cells due to their hydrophilic nature and large molecular structure. In many cases, biological antisense activity can

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only be achieved in the presence of transfer vectors such as cationic lipids and liposomes. The obviousness of this problem, however, does not necessarily diminish the potential use of ONs *in vivo*, and there are few examples of successful *in vivo* treatment in the absence of specialized delivery systems [44, [Wickstrom et al, Cancer Res. 52: 6741 (1992)], 45 [Kitajima et al, Science 258: 1792 (1992)]]]. Much effort has been made with some success to chemically modify ON and to develop carrier vectors for effective delivery of antisense ONs.

Were appellant's arguments correct, section 3 of the Rojanasakul article would be unnecessary. The article by Gura echoes what Rojanasakul reports. Appellant's *ad hominem* criticisms of Gura are given no weight as explained hereinabove in connection with the Crooke declaration. Appellant goes on (paper no. 73, filed June 21, 2002, pages 23-24) to use Gura to support the notion that the claimed invention is enabled using mathematical values from *In re Wands* (8 USPQ2d 1400, Fed. Cir. 1988). Appellant points out that in *Wands* 4 of 143 (2.8%) hybridomas successfully produced monoclonal antibodies. This much is correct. Appellant then uses the report in Rojanasakul that 1-2% of oligonucleotides administered to cells in culture become cell-associated. This much is correct too. Appellant then somehow concludes that *Wands* along with Gura and Rojanasakul weighs in favor of enablement. This conclusion is inexplicable. What *Wands* deals with is a success rate of 2.8%, *i.e.* 2.8% of hybridomas produced were 100% successful in producing the monoclonal antibodies that were the subject of the invention. The court found that this was an acceptable success rate to support enablement. Appellant has not pointed to any success rate at all and somehow considers the 1-2% "cell-association" (not necessarily cellular entry) of oligonucleotides in cells in culture, with no report of any success of the claimed method at all *in vivo*, to be close enough to the 2.8% success rate in *Wands* to pass the enablement test. Such rough and unwarranted equivalency of similar percentages of dissimilar molecules involved in incomparable biological processes and in unlike states (*i.e.* rate of cell-association compared to success rate of monoclonal antibody production) cannot blindly be translated from one situation to another. There is no magic *Wands* percentage threshold to prove enablement. Appellant misquotes Rojanasakul as stating there are "examples of successful *in vivo* treatment in the absence of specialized delivery systems." The complete and correct quote runs this way:

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The obviousness of this problem, however, does not necessarily diminish the potential use of ONs *in vivo*, and there are few examples of successful *in vivo* treatment in the absence of specialized delivery systems [44, [Wickstrom et al, Cancer Res. 52: 6741 (1992)], 45 [Kitajima et al, Science 258: 1792 (1992)]].

The “few” successful examples cited by Rojanasakul were published in 1992, more than ten years after the effective filing date of the instant application. The sense given in Rojanasakul is directed at the potential of *in vivo* antisense (indeed, Rojanasakul uses the term “potential”) as of 1996 rather than the notion that antisense methods had had an established *in vivo* use as early as 1981 (the effective filing date of the instant application). Indeed, the review article by Crooke et al (Annu. Rev. Pharmacol. Toxicol. 36: 107 (1996)) in Table 2, page 116 reports the earliest results of the use of antisense oligonucleotides in animal models to be in 1989 (Kulka et al, Proc. Natl. Acad. Sci. USA 86: 6868 (1989)) with all other reports coming in 1991 to 1995. Additionally, appellant cites Phillips et al (1994), Mercola et al (1995), Putnam et al (1996), and Hijiya et al (1994) (paper no. 73, filed June 21, 2002 pages 24-25) as supporting enablement, but appellant establishes no connection between the actual methods used in any of these references and what is taught in the instant application. Additionally, each of these references was published more than a decade following the effective filing date. It is again noted that Hijiya et al, cited by appellant to support the position that the instant application is enabled, characterizes this art as one that “remains in its scientific infancy” as late as 1994:

Knowledge concerning DNA uptake mechanisms, intracellular ODN [oligodeoxyribonucleotide] trafficking, mRNA disruption mechanisms, and, of equal importance, how apparent resistance develops will all contribute significantly to the effective pharmaceutical use of these compounds. Accordingly, while this area remains in its scientific infancy, the *in vivo* studies and those of our colleagues . . . convince us that modulation of gene expression with antisense DNA is a therapeutic strategy worth pursuing.

Thus, the published evidence in this record indicates that even though the method of Tullis was published in 1983, it was several years before highly skilled artisans in an active area of research published any result of success in getting the method to work. This evidence weighs heavily against the idea that the

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instant application provides enough guidance for one of skill in the art to practice the claimed invention as early as the effective filing date of the instant application.

Appellant then argues the issue of *in vivo* stability of the antisense oligonucleotides to be administered (paper no. 73, filed June 21, 2002, pages 25-28 and Brief filed October 18, 2004, pages 12-13). The statements of Tullis referred to above speak against the workability of the method *in vivo* by the "just add more" method now advocated by appellant. There is no disclosure of the use of unmodified oligonucleotides *in vivo* nor is there any evidence that the inventor contemplated the use of unmodified oligonucleotides *in vivo*. The discussion of the post-filing-date remarks of Tullis et al and Tullis hereinabove are incorporated here. Likewise, the discussion of the use of stabilized oligonucleotides other than phosphotriesters hereinabove is incorporated here. Appellant's argument in connection with Rojanasakul (paper no. 73, filed June 21, 2002, page 27) are most unconvincing because the part of Rojanasakul alluded to and appellant's argument are in connection with the use of the method on cells in culture. The issue is directed to the use of the method *in vivo*. Appellant already has an issued U.S. Patent (5,919,619) that claims the method used on cells in culture. The discussions of Gura hereinabove are incorporated here. Additionally, appellant's argument in connection with Gura (paper no. 73, filed June 21, 2002, pages 27-28) is most unconvincing because although Gura reports that some biological effects are seen upon administration of oligonucleotides, Gura goes on to explain that the oligonucleotides do not always work by the expected mechanism (*i.e.* the mechanism disclosed in the instant application) and that it is difficult to tell what mechanism causes the biological effect. This idea is corroborated by Branch. Appellant's arguments in connection with the examiner failing to carry the burden of showing that cell culture systems cannot be compared to *in vivo* systems (paper no. 73, filed June 21, 2002, page 28) are not convincing for the reasons given hereinabove in connection with the issue of cellular uptake of oligonucleotides.

Appellant argues (paper no. 73, filed June 21, 2002, pages 29-32) that the instant specification provides adequate guidance in connection with the specificity of *in vivo* hybridization of oligonucleotides. Appellant's argument regarding the number of random combinations in a genome are not relevant to the

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basis of the rejection because the rejection is based upon the potential effect of changing the backbone of the oligonucleotides from a phosphodiester backbone to some other type of backbone to achieve increased stability of the oligonucleotides upon specificity of hybridization. That this was not only a concern among those of skill in the art, but was incompletely understood even as late as 1988 (Rojanasakul reference number 54, Stein et al, Gene 72: 333 (1988)) is evidenced by Rojanasakul (*e.g.*, page 119 "these [phosphorothioate] compounds, when compared to their unmodified counterparts, tend to have lower binding affinity to their target sequences due, possibly, to diastereomer formation [54]."). Appellant's arguments in connection with Summerton (1979) are most unconvincing (paper no. 73, filed June 21, 2002, pages 29-30). Appellant asserts that double-stranded oligonucleotides are available for the method of the instant application, yet appellant provides no evidence for this conclusion. There is no hint in the application that double-stranded oligonucleotides will work in the claimed method. In fact, the purported mechanism of action disclosed in the instant application would preclude one of skill in the art from considering the use of double stranded oligonucleotides because such molecules are not free to bind with the target mRNA without the two strands first being separated. The application does not hint at how such strand separation is to be achieved after *in vivo* administration of the double-stranded oligonucleotide. The discussions of Gura, Rojanasakul, Phillips et al, Hijiya et al, Mercola et al, and Putnam hereinabove are incorporated here. None of these references suggests that as of the effective filing date of the instant application, one of skill in the art would know that changes in the backbone of oligonucleotides would not affect specificity of hybridization *in vivo*. Additionally, Branch reports that many non-specific effects result upon administration of oligonucleotides both on cells in culture and *in vivo*.

The declaration by Dr. Hecht filed March 7, 2003 has been considered. This declaration is not persuasive for the following reasons.

- (a) Declarant characterizes each of the Gura, Rojanasakul, and Hijiya et al references narrowly as being directed toward the "immediate clinical applicability of *in vivo* use of antisense technology" (section 5 of the declaration). This

characterization is unduly narrow since these references all address the broader issues of uptake, stability, and specificity of hybridization of the antisense agent to its intended target (*e.g.*, see the summary under the title in Gura, sections 3 and 4 of Rojanasakul, and the last paragraph of text on page 4503 of Hijiya et al. Declarant's arguments in connection with potential toxic effects of antisense agents are irrelevant because the rejection is not based on the existence of potential toxic effects, but is based on the lack of an adequate in the instant application as to how to practice the claimed invention *in vivo*. Declarant makes no correlation between any of the work described in the published literature and the disclosure in the instant application. Declarant asserts (page 6, first full paragraph that "successes achieved in the field of antisense technology have been witnessed, thereby ratifying the views of proponents of antisense at the time of the invention and silencing, indeed converting, many critics to what is clearly the correct view: antisense works *in vivo* as taught by the present application." Declarant does not support this assertion with any named critic who has been either "silenced" or "converted" and does not make any correlation or connection between any successful *in vivo* antisense trial and any *in vivo* antisense method disclosed in the instant application. Without such connections, no number of citations of successful *in vivo* antisense trials published subsequent to appellant's effective filing date can support the notion that the instant application provides an enabling disclosure within the meaning of 35 U.S.C. § 112, first paragraph. Thus, none of Exhibits 4-7 nor their combination can convince that the application provides an enabling disclosure.

- (b) Section 6 of the declaration is not convincing. First, the discussion of potential toxic effects is not relevant because the rejection is not based on the existence of potential toxic effects. Second, declarant offers his opinion as to why

researchers did not publish *in vivo* antisense results before the early 1990s (about ten years after the effective filing date of the instant application). These reasons are merely declarant's opinion which opinion is supported only by general views as to the academic research environment and the corporate research environment. Without some factual information, these opinions and general observations of only one individual cannot convince that these reasons were the reason for the failure of any and all groups of researchers to publish an account of *in vivo* antisense working. It is reiterated here that this has been an active field of research since its inception (for example, see the numerous references cited in Rojanasakul). Declarant has not established that he has any special knowledge that puts him in a position to speak for all academic scientists in the field regarding the reasons for such non-publication. Declarant's speculations regarding the reasons for lack of publication by academics are not convincing.

- (c) Similarly to the discussion in (b) immediately above, declarant has not established that he is in a position to speak for all pharmaceutical companies in connection with their strategies for pursuing or not pursuing research in the filed of antisense at the time in question (section 7 of the declaration). Anecdotes and generalizations cannot substitute for fact in an attempt to convince one that the instant application contains an enabling disclosure within the meaning of 35 U.S.C. § 112, first paragraph.

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For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Primary Examiner
Art Unit 1634


1/28/05

January 28, 2005

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Attachments:

- A. Summerton, J. theor. Biol. 78: 77 (1979)
- B. U.S. Patent No. 5,023,243, patented file paper no. 9, filed February 9, 1984.
- C. U.S. Patent No. 5,023,243, patented file paper no. 12, interview summary record, November 15, 1984.
- D. U.S. Patent No. 5,023,243, patented file paper no. 14, filed December 7, 1984.
- E. U.S. Patent No. 5,023,243, patented file paper no. 17, interview summary record, October 18, 1985.
- F. U.S. Patent No. 5,023,243, patented file paper no. 21, filed April 4, 1986.

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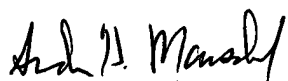
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- G. Mercola et al, Cancer Gene Therapy 2 (1), 47 (1995)